Symposium Title: Neurophysiological Indicators of ASD-Related Behavioral Phenotypes

Chair: Abigail L. Hogan

Discussant: Shafali Jeste

Overview: Neurophysiological methods, such as electroencephalogram (EEG) and event-related potential (ERP) provide unique insight into the neurobiological mechanisms that underpin the core behavioral deficits of autism spectrum disorder (ASD). This symposium includes three complementary studies that investigate the relationship between neurophysiological indicators and a range of ASD-related phenotypes, from social-communicative behavior to sensory processing. The first presentation investigates the relationship between ERP responses during infancy and ASD symptoms later in childhood in two distinct risk groups – infants with fragile X syndrome (FXS) and siblings of children with ASD. The second study investigates the association between ERP responses to social and nonsocial stimuli and ASD symptoms in preschool-aged siblings of children with ASD who do not have ASD themselves. The third presentation utilizes auditory ERPs to define distinct sensory processing subgroups of children with ASD. This symposium, which highlights work from early career scientists across several institutions and disciplines, represents critical advancements in characterizing potential neurobiological mechanisms that contribute to behavioral differences in children with ASD and children with elevated genetic liability to ASD.

Paper 1 of 3

Paper title: Infant ERP Responses and Later Emerging Symptoms of ASD in Etiologically-Distinct High-Risk Groups

Authors: Maggie W. Guy, Abigail L. Hogan, John E. Richards, & Jane E. Roberts

Introduction: Past research has shown that etiologically-distinct groups of infants at high-risk of autism spectrum disorders (ASD) demonstrate differences in electrophysiological responses to social and non-social stimuli at 12 months of age. The current study aimed to increase understanding of how differences in infant event-related potentials (ERPs) across infant siblings of children with autism (ASIBs) and infants diagnosed with fragile X syndrome (FXS) are associated with clinical outcomes in early childhood. The study was conducted in two stages, 1) we analyzed ERP responses to faces and toys in three groups of 12-month-old infants (ASIBs, infants with FXS, and low-risk control (LRC) infants), 2) we examined relations between these responses and scores on the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) and diagnostic outcomes at 36-48 months of age.

Methods: Fifty participants were included in the current study. At 12 months of age, 18 ASIBs (15 M), 14 infants with FXS (7 M), and 18 LRC infants (14 M) participated in the ERP study. Participants passively viewed photographs of their mother’s face, a stranger’s face, their toy, and a novel toy while EEG was recorded. Amplitude of the N290 and P400 ERP components, associated with infant face processing, were measured at lateral temporal, parietal, and occipital electrodes. Amplitude of the Nc ERP component, associated with attention allocation, was measured at midline frontal and central electrode sites. In early childhood, diagnostic outcomes were determined using the clinical best estimate (CBE) approach. CBE assessments were conducted by trained clinicians and utilized information collected through social-behavioral assessments of the child, as well as parent interviews. Clinical assessments were completed in participants approximately 36 months of age. If an assessment at that time could not be arranged, we used assessments conducted at 48 months or later if available, and 24 months of age if necessary. The mean age of clinical assessment across groups was equivalent (ASIB: \(M = 48.00\) months, FXS: \(M = 47.14\) months, LRC: \(M = 44.67\) months). The ADOS was one measure that was included in the battery of assessments completed, and calibrated severity scores

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on the ADOS were examined in relation to infant ERP responses. Amplitude of the N290, P400, and Nc ERP components in response to faces and toys were examined in association with Overall, Social Affect (SA), and Repetitive Behavior (RB) ADOS scores using ANCOVAs and regressions.

Results: The CBE results showed that eight participants were diagnosed with ASD and an additional 11 participants were diagnosed with non-ASD developmental delay (DD); the remaining 31 participants demonstrated no clinical symptoms or subthreshold ASD symptoms (ASIB group: 3 ASD, 3 DD; FXS group: 4 ASD, 5 DD; LRC group: 1 ASD, 3 DD).

Analyses investigating relations between infant risk group, Overall, SA, and RB ADOS scores, and ERP amplitude revealed significant effects for the N290 and P400 ERP components. There was a significant interaction between participant group, stimulus type, and Overall ADOS score, $F(2, 4680) = 11.02, p < 0.0001$, as well as SA score, $F(2, 4680) = 13.45, p < 0.0001$, on N290 amplitude. For ASIBs, greater (more negative) amplitude N290 to faces and toys was associated with higher Overall ADOS scores and higher scores on the SA scale. Participants with FXS also showed greater amplitude of N290 associated with Overall ADOS scores, but only for ERP responses to faces. Participants in the LRC group showed the opposite pattern of results, as decreased N290 amplitude in response to faces was associated with higher Overall ADOS scores and higher scores on the SA scale. There was also a significant interaction between participant group, stimulus type, and overall ADOS score, $F(2, 3898) = 5.64, p = 0.0036$, as well as SA score, $F(2, 3898) = 3.57, p = 0.0282$, on P400 amplitude. At the P400, participants with FXS showed that greater (more positive) amplitude responses to faces and toys were associated with higher Overall ADOS scores and higher scores on the SA scale. For ASIBs, decreased amplitude P400 responses to toys were associated with higher Overall ADOS scores and higher scores on the SA scale. In LRC participants, a decreased P400 amplitude in response to faces was associated with higher Overall ADOS scores.

Discussion: Our analyses revealed relations between ERP responses at 12 months of age and ADOS scores in early childhood. Interestingly, these relations varied across groups based on ASD risk as assessed in infancy. Previous research has indicated that infants with FXS show enhanced ERP activity in to faces relative to ASIB and LRC groups, while ASIBs showed more muted ERP responses. The current study reveals that the increased in ERP amplitude responses exhibited in infants with FXS may be associated with later emerging symptoms of ASD. The relations between infant ASIBs’ ERP responses and later emerging ASD symptoms are less straightforward and do not show the face specificity demonstrated by the FXS group.

References/Citations:

Paper Title: Associations between ERP Responses to Social Stimuli and ASD Symptoms in “Unaffected” Siblings of Children with Autism Spectrum Disorder

Authors: Abigail L. Hogan¹, Conner Black¹, Jessica Escorcia³, Margaret Guy², John E. Richards¹, & Jane E. Roberts¹

Introduction: Siblings of children with autism spectrum disorder (ASD), even those who are not later diagnosed with ASD themselves (non-ASD ASIBs), often exhibit elevated ASD-related social-behavioral difficulties¹-³. Few studies have fully characterized these behavioral differences or investigated the underlying neurophysiological mechanisms that may contribute to them. The objectives of the present study were to a) characterize ERP responses to social and non-social stimuli and b) investigate the relationship between ERP responses and downstream social-behavioral phenotypes in non-ASD ASIBs and typically developing (TD) controls.
Methods: Twenty-six participants were included in this study (non-ASD ASIBs: n = 11, 81.8% male; TD controls: n = 15, 100% male). Groups were similar on chronological age (t(24) -0.81, p = .427), with non-ASD ASIBs ranging from 4.18 to 8.32 years [M(SD) = 5.96(1.25)] and TD controls ranging from 4.06 to 7.09 years [M(SD) = 5.60(1.05)]. Non-ASD ASIBs had an older sibling with a diagnosis of ASD but were not diagnosed with ASD themselves. TD controls had no family history of ASD. Participants completed an EEG experiment in which they passively viewed upright faces, inverted faces, upright houses, and inverted houses. The latency and amplitude of P1, which corresponds with the processing of low-level visual features, was measured at the central occipital (O2) electrodes. The latency and amplitude of N170, which corresponds to early structural encoding of facial features, was measured at posterior lateral electrodes (P8). Participants also completed a battery of social-behavioral measures that included the Autism Diagnostic Observation Schedule – Second Edition (ADOS-2)4, the Childhood Autism Rating Scale (CARS)5, and the Social Responsiveness Scale (SRS)6. Latencies and amplitudes for the P1 and N170 ERP components were examined across conditions and groups in repeated measures ANOVAs. The correlations between ERP responses and social-behavioral variables were also investigated using Pearson correlations.

Results: No main or interaction effects were observed for P1 latency or amplitude, in that similar P1 responses were exhibited across groups for each condition. For N170 latency, no main or interaction effects were observed. For N170 amplitude, the main effect of condition was significant, F(3, 69) = 10.22, p < .001, with the faces eliciting larger amplitudes than the houses, ps < .037, but no main effect of group or group by condition interaction was present. In TD controls, P1 and N170 latencies and amplitudes were not significantly correlated with any social-behavioral measures. In non-ASD ASIBs, however, several significant correlations emerged. N170 latency to upright faces was significantly correlated with the ADOS-2 Social Affect severity score, r = -.71, p = .021 and marginally correlated with the CARS total score, r = -.620, p = .056 and SRS total score, r = -.63, p = .068. N170 amplitude to inverted faces was correlated with the ADOS-2 Social Affect severity score, r = -.66, p = .050 and the SRS total score, r = -.80, p = .009, whereas N170 amplitude to upright faces was marginally correlated with the ADOS-2 Social Affect severity score, r = -.62, p = .057, and SRS total score, r = -.62, p = .076. Interestingly, N170 amplitude to inverted houses was also correlated with ADOS-2 Social Affect severity score, r = -.69, p = .038, and CARS total score, r = -.87, p = .002.

Discussion: These results reveal that ERP responses to social and non-social stimuli are more similar than they are different between non-ASD ASIBs and TD controls. However, specific patterns of correlations between ERP responses and ASD symptoms in non-ASD ASIBs suggest that neurophysiological functioning may be closely tied to ASD-related behavior in those at elevated genetic risk for ASD.

References/Citations:

Title: Investigating Sensory Subtypes Using Auditory ERPs in Young Children with Autism and Typical Development

Authors: Patrick Dwyer4,5, Xiaodong Wang6, Rosanna De Meo-Monteil5, Fushing Hsieh5, Clifford Saron4,7, & Susan M. Rivera4,5,7

Introduction: Sensory processing differences in autism are related to quality of life (Lin & Huang, 2017). These sensory processing differences are heterogeneous (Uljarević et al., 2017), but prior attempts to define sensory subtypes in autism have
relied on responses to questionnaires. Furthermore, only two such studies included participants with typical development (TD) (Elwin et al., 2017; Little et al., 2017), making it difficult to contextualize heterogeneity in autism. The present study uses heatmap-based clustering of event-related potentials (ERPs) to define sensory subtypes in a large sample of young children with autism or TD.

**Method:** ERPs to auditory stimuli were investigated in 81 participants with TD (52 male, $M_{\text{age}} = 37.09$ mos, $SD_{\text{age}} = 6.46$ mos) and 132 with autism (111 male, $M_{\text{age}} = 38.51$ mos, $SD_{\text{age}} = 6.04$ mos). While watching a quiet video, participants heard, via headphones, brief tones randomly varying in loudness between 50, 60, 70 and 80 dB (200-300 trials/intensity) at an ISI randomly varying between 1-2s. 61-channel EEGs were sampled at 1000 Hz. The global field power (GFP) was used as an index of neural response strength. Hierarchical clustering was used to define subgroups while preserving temporal information. Separately within two time windows, each participant’s GFP values in each loudness condition at every millisecond were entered into heatmaps and clustered using Ward’s method. The early time window was defined separately in each loudness condition as the window spanning the time-points on either side of GFP peak where GFP values equaled 85% of the peak (50 dB: 101-152ms; 60 dB: 90-141ms; 70 dB: 79-133ms; 80 dB: 79-120ms). The late time window was defined as the period between the end of the early window and 349ms. Participants’ parents completed the Short Sensory Profile (SSP).

**Results:** In each time window, five clusters were defined. In the early window, these included CE1 (i.e., “Cluster, Early, 1”), with strong responses increasing in strength with loudness condition. CE2 had even stronger GFP, particularly in response to softer stimuli; this group had a large number of participants with autism. CE3 was characterized by weak responses in all loudness conditions, while responses in CE4 were slightly stronger. Overall, responses in CE5 were similar in strength to CE4, but with a stronger 50 dB response; this group was dominated by participants with TD.

In the late time window, the five clusters included CL1 (i.e., “Cluster, Late, 1”), with middling-strength responses and a preponderance of participants with TD. Responses in CL2 were somewhat stronger. CL3 had responses of similar strength to CL2 but with a very strong response to 50 dB stimuli, while CL4 had even stronger GFP, especially in response to louder stimuli; both CL3 and CL4 were dominated by participants with autism. CL5 was characterized by weak GFP in all loudness conditions.

Clusters were compared on chronological age and SSP scores. Participants with TD in CL5 trended towards being young, while participants with autism in CL2 were older than those in CL3. No SSP effects survived corrections for multiple comparisons.

**Discussion:** The present study reveals considerable heterogeneity in sensory processing at the neural level. Although there was substantial overlap between participants with autism and TD, one diagnostic group predominated in some clusters. Interestingly, while participants with TD predominated in one cluster with an expected loudness-dependent pattern (CL1), they were also found in a cluster with an odd response pattern (CE5). Most clusters predominated by participants with autism (CE2, CL3, CL4) appeared to show stronger responses. Clusters did not differ in SSP scores, raising questions about the relationship between neural processing and sensory behaviours and questions regarding appropriate methods of assessing sensory experiences.

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**References/Citations:**
